



TRANSMITTED BY FACSIMILE

Catherine K. Clark
Director, US Regulatory Affairs
GlaxoSmithKline
One Franklin Plaza, PO Box 7929
Philadelphia, PA 19101

RE: NDA #21-071 AVANDIA (rosiglitazone maleate) Tablets
NDA #21-410 AVANDAMET (rosiglitazone maleate and metformin hydrochloride) Tablets
NDA #21-700 AVANDARYL (rosiglitazone maleate and glimepiride) Tablets
NDA #21-319 AVODART (dutasteride) Soft Gelatin Tablets
NDA #22-012 COREG CR (carvedilol phosphate) Extended-release Capsules
NDA #22-059 TYKERB (lapatinib) Tablets
MACMIS ID #17317

Dear Ms. Clark:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed GlaxoSmithKline's sponsored links on internet search engines (e.g., Google.com) for the following products: AVANDIA (rosiglitazone maleate) Tablets (Avandia), AVANDAMET (rosiglitazone maleate and metformin hydrochloride) Tablets (Avandamet), AVANDARYL (rosiglitazone maleate and glimepiride) Tablets (Avandaryl), AVODART (dutasteride) Soft Gelatin Tablets (Avodart), COREG CR (carvedilol phosphate) Extended-release Capsules (Coreg CR), and TYKERB (lapatinib) Tablets (Tykerb). The sponsored links cited in this letter are misleading because they make representations and/or suggestions about the efficacy of Avandia, Avandamet, Avandaryl, Avodart, Coreg CR, and Tykerb, but fail to communicate **any** risk information associated with the use of these drugs. In addition, the sponsored links inadequately communicate the drugs' indications and fail to use the required established name. Thus, the sponsored links misbrand the drugs in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. See 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 201.10(g)(1), 202.1(b)(1), (e)(3)(i), (ii) & (e)(6)(i).

Background

Avandia

According to its FDA-approved product labeling (PI), Avandia is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The PI includes important limitations to use, such that Avandia should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, the co-administration of Avandia and insulin is not recommended, and the use of Avandia with nitrates is also not recommended.

Avandia is associated with a number of risks, as reflected in the Boxed Warning, Contraindications, Warnings and Precautions, and Adverse Reactions sections of its PI.

Avandamet

According to its FDA-approved PI, Avandamet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and metformin therapy is appropriate. The PI includes important limitations to use, such that Avandamet should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, the co-administration of Avandamet and insulin is not recommended, and the use of Avandamet with nitrates is also not recommended.

Avandamet is associated with a number of risks, as reflected in the Boxed Warning, Contraindications, Warnings and Precautions, and Adverse Reactions sections of its PI.

Avandaryl

According to its FDA-approved PI, Avandaryl is indicated as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and glimepiride therapy is appropriate. The PI includes important limitations to use, such that Avandaryl should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, the co-administration of Avandaryl and insulin is not recommended, and the use of Avandaryl with nitrates is also not recommended.

Avandaryl is associated with a number of risks, as reflected in the Boxed Warning, Contraindications, Warnings and Precautions, and Adverse Reactions sections of its PI.

Avodart

According to its FDA-approved PI, Avodart is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention (AUR), and reduce the risk of the need for BPH-related surgery.

Avodart is associated with a number of risks, as reflected in the Contraindications, Warnings and Precautions, and Adverse Reactions sections of its PI.

Coreg CR

According to its FDA-approved PI, Coreg CR is indicated, among other things, for the treatment of essential hypertension. Coreg CR can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Coreg CR is associated with a number of risks, as reflected in the Contraindications, Warnings and Precautions (including bolded warnings), and Adverse Reactions sections of its PI.

Tykerb

According to its FDA-approved PI, Tykerb is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors

overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

Tykerb is associated with a number of risks, as reflected in the Boxed Warning, Warnings and Precautions, and Adverse Reactions sections of its PI.

Omission of Risk Information

Promotional materials, other than reminder pieces, which include the name of the drug product but do not include indications or other representations or suggestions relative to the drug product (see 21 CFR 200.200, 201.100(f), 202.1(e)(2)(i)), are required to disclose risk and other information about the drug. Such materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The sponsored links present the following claims:

- Avandia® Official Site
www.Avandia.com See How Avandia® Can Help Patients Living with Type 2 Diabetes
- Avandamet® Official Site
www.AVANDAMET.com Type 2 Diabetes Can Be Tough Learn About A Diabetes Medicine
- Avandaryl® Official Site
www.AVANDARYL.com Type 2 Diabetes Can Be Tough Find Out How Avandaryl® Can Help
- Prostate Health
www.Avodart.com Important Information About Determining Your Prostate Health
- Blood Pressure Facts
www.COREGCR.com Learn Why Blood Pressure Is Called The “Silent Killer” & How to Manage
- Metastatic Breast Cancer
www.TYKERB.com Discover more treatment options for HER2+ metastatic breast cancer

These sponsored links make representations and/or suggestions about the efficacy of Avandia, Avandamet, Avandaryl, Avodart, Coreg CR, and Tykerb, respectively, but fail to communicate **any** risk information. This omission of risk information is particularly concerning as four of the products, Avandia, Avandamet, Avandaryl, and Tykerb, have Boxed Warnings. For promotional materials to be truthful and non-misleading, they must contain risk information in each part as necessary to qualify any claims made about the drug.

By omitting the most serious and frequently occurring risks associated with the drugs

promoted in the links above, the sponsored links misleadingly suggest that Avandia, Avandamet, Avandaryl, Avodart, Coreg CR, and Tykerb are safer than has been demonstrated. We note that these sponsored links contain a link to the products' websites. However, this is insufficient to mitigate the misleading omission of risk information from these promotional materials.

Inadequate Communication of Indication

The above sponsored links provide very brief statements about what the drugs are for; however, these statements are incomplete and misleading, suggesting that Avandia, Avandamet, Avandaryl, Avodart, Coreg CR, and Tykerb, respectively, are useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

Specifically, the sponsored links for Avandia, Avandamet, and Avandaryl broaden the indication for these drugs by failing to reveal that they are only indicated as **adjunct** therapies to diet and exercise to improve glycemic control in patients with type 2 diabetes. Additionally, the sponsored links fail to include any of the important limitations of use from the Indications and Usage section of the PI for Avandia, Avandamet and Avandaryl.

Similarly, the sponsored link for Avodart misleadingly broadens the indication for Avodart by implying that the drug is approved to generally help improve prostate health ("Important Information about Determining your Prostate Health" along with the drug name), when this is not the case. Rather, Avodart is only indicated for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery.

Moreover, the sponsored link for Coreg CR misleadingly broadens the indication for Coreg CR by implying that the drug is indicated for the management of all blood pressure ailments ("Learn Why Blood Pressure Is Called The 'Silent Killer' & How to Manage"), when this is not the case. Rather, Coreg CR's indication is limited to the treatment of essential hypertension.

Finally, the sponsored link for Tykerb misleadingly broadens the indication for Tykerb by implying that all patients with HER2+ metastatic breast cancer are candidates for Tykerb therapy ("Discover more treatment options for HER2+ metastatic breast cancer"), when this is not the case. Rather, Tykerb is indicated for the treatment of advanced or metastatic breast cancer when tumors overexpress HER2, and when prior therapy including an anthracycline, a taxane, and trastuzumab has been received. Additionally, the link fails to reveal that Tykerb is only indicated for use in combination therapy.

Failure to Use Required Established Name

None of the sponsored links present the full established name of the drugs being promoted, despite the requirement to do so. See 21 CFR 201.10(g)(1) & 202.1(b)(1).

Conclusions and Requested Action

For the reasons discussed above, the sponsored links misbrand Avandia, Avandamet, Avandaryl, Avodart, Coreg CR, and Tykerb, in violation of the Act and FDA regulations. See 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 201.10(g)(1), 202.1(b)(1), (e)(3)(i), (ii) & (e)(6)(i).

DDMAC requests that GlaxoSmithKline immediately cease the dissemination of violative promotional materials for Avandia, Avandamet, Avandaryl, Avodart, Coreg CR, and Tykerb, such as those described above. Please submit a written response to this letter on or before April 9, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for these drugs as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such materials. Finally, we encourage you to review your promotional materials for the other prescription drug products that GlaxoSmithKline promotes in the United States and to discontinue or revise any materials with the same or similar violations, and request that your response address this issue as well.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #17317 in addition to the NDA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Avandia, Avandamet, Avandaryl, Avodart, Coreg CR, and Tykerb comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Michael Sauers
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Michael A Sauers
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